PATENT COOPERATIOI REATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 16 December 1999 (16.12.99)	
International application No. PCT/US99/08205	**Applicant's or agent's file reference** MGH-002.1PCT
International filing date (day/month/year) 15 April 1999 (15.04.99)	**Priority date** (day/month/year) 16 April 1998 (16.04.98)
Applicant FAUSTMAN, Denise, L.	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

08 November 1999 (08.11.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer A. Karkachi
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference MGH-002.1PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/08205	International filing date *(day/month/year)* 15 APRIL 1999	Priority date *(day/month/year)* 16 APRIL 1998
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant THE GENERAL HOSPITAL CORPORATION		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [ ] Non-establishment of report with regard to novelty, inventive step or industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [X] Certain observations on the international application

Date of submission of the demand	Date of completion of this report
08 NOVEMBER 1999	23 OCTOBER 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ANNE MARIE S. BECKERLEG Telephone No. (703) 308-0196

Form PCT/IPEA/409 (cover sheet) (July 1998) ★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/08205

I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-34 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the claims:
pages 35-37 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the drawings:
pages 1-16 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the sequence listing part of the description:
pages 1-20 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[X] contained in the international application in printed form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [X] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/08205

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	(Please See supplemental sheet)	YES
	Claims	(Please See supplemental sheet)	NO
Inventive Step (IS)	Claims	(Please See supplemental sheet)	YES
	Claims	(Please See supplemental sheet)	NO
Industrial Applicability (IA)	Claims	(Please See supplemental sheet)	YES
	Claims	(Please See supplemental sheet)	NO

2. citations and explanations (Rule 70.7)

Claims 1-2 and 31-32 lack novelty under PCT Article 33(2) and inventive step under PCT Article 33(3) as being anticipated and made obvious by Bahram et al. The applicant claims an isolated nucleic acid encoding a TAP1 or TAP2 splice variant, an isolated nucleic acid comprising a polynucleotide sequence that is at least 95% identical to a polynucleotide having the polypeptide sequence of SEQ ID NO. 2, and TAP1 or TAP2 splice variant proteins which have the ability to form heterodimers with either TAP2 or TAP1 respectively. It is noted that TAP1 and TAP2 have been identified in the literature by a variety of names including RING1 and RING2 and PSF1 and PSF2. It is further noted that the applicant's claim 1 reads on the "wild type" sequence as the this sequence is one of two or more splice variants of a single gene.

Bahram et al. teach an isolated nucleic acid, designated PSF 2, which, as the wild type sequence of TAP2, is naturally a splice variant (Bahram et al., supra, page 10095, Figure 2). Further the reported sequence of PSF2 is greater than 97% identical to the polynucleotide sequence that encodes for SEQ ID NO. 2. In addition, Bahram et al. also teaches the wild type TAP1 and TAP2 proteins which form heterodimers with TAP2 or TAP1 respectively. Thus, by teaching all the elements of the claims, Bahram et al. clearly anticipates and makes obvious the instant invention as claimed.

Claims 1-2, 7-8, 13-14, 19-20, and 25-26 lack novelty under PCT Article 33(2) and inventive step under PCT Article 33(3) as being anticipated and made obvious by Wang et al. The applicant claims an isolated nucleic acid encoding a TAP1 or TAP2 splice variant and an isolated nucleic acid comprising a polynucleotide sequence that is at least 95% identical to a polynucleotide having the polypeptide sequence of SEQ ID NO. 2. The applicant further claims expression vectors encoding said nucleic acids, host cells transfected with said vectors, and methods of producing TAP proteins and altering transport of peptides comprising transfecting cells with said vector.

Wang et al. teaches an expression vector encoding the human TAP2 gene, and the transfection of human B cells from patients with IDDM wherein the expression of the TAP2 protein results in (Continued on Supplemental Sheet.)

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The description is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 5 because it fails to adequately enable practice of the claimed invention for the following reason. The description discloses splice variants of the peptide transporter genes TAP1 and TAP2 designated TAP1iso, TAP1iso2, TAP2iso, and TAP2iso2. The description further discloses that TAP splice variants function by forming heterodimers with either wild type TAP proteins or other splice variants, thereby forming peptide transporter complexes with altered capacity for transporting certain peptides from the cytoplasm to the endoplasmic reticulum. The description further states that the loss of expression of one or more TAP1 or 2 splice variants may be associated with certain autoimmune disorders and discloses the treatment of autoimmune disease by administration of expression vectors encoding said TAP1 or 2 splice variants.

The description does not provide an enabling disclosure for any and all splice variants of TAP1 and TAP2 from any and all species. The description focuses primarily on the human TAP2 splice variant TAP2iso, which lacks exon 11 found in wild type human TAP2, but contains a novel exon 12. The description provides several examples demonstrating that cDNA encoding human TAP2iso, exons 1-10 and 12, produces a TAP2iso protein that is capable of forming a heterodimer with wild type human TAP1, and is further capable of transporting peptides across the ER membrane resulting in the surface expression of peptide loaded MHC class I molecules on the cell surface of T2 cells transfected with both TAP1 and TAP2iso. The description's disclosure in regards to the existence of further splice variants of human TAP2 is limited to the detection by PCR of an additional band in some but not all normal human PBLs using a forward primer derived from TAP2 exon 9 and a reverse primer from TAP2 intron 10. For human TAP1, the description's examples goes one step further and provides sequencing data of the additional bands amplified by the TAP1 exon 9 and TAP1 intron 10 primers. In regards to the additional band identified for TAP2, the description speculates but provides not concrete evidence that the extra length of the band is the result of a novel splicing event in which a portion of intron 10 is left attached to exons 1-10. Further, the description does not provide guidance as to the portion or sequence of intron 10 forms the 3' end of the mRNA. In regards to the additional TAP1 bands, again, the description does not provide adequate guidance as to the length and sequence of the portion of intron 10 spliced to the 3' end of exon 10. Because the applicants use a single primer from intron 10 it cannot be determined that the splice variants identified by PCR do not contain additional sequences at the 3' end of the original mRNA transcripts. More importantly, the description does not provide (Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

CLASSIFICATION:
The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(7): C07H 21/04; C12N 15/11, 15/63, 15/85, 1/21; C07K 5/00, 14/00, 16/00; A61K 48/00 and US Cl.: 536/23.1; 435/320.1, 325, 252.3; 530/300, 350, 387.1; 514/44

I. BASIS OF REPORT:

5. (Some) amendments are considered to go beyond the disclosure as filed:
NONE

V. 1. REASONED STATEMENTS:
The report as to Novelty was positive (YES) with respect to claims 3-6, 9-12, 15-18, 21-24, 27-30, 33-42.
The report as to Novelty was negative (NO) with respect to claims 1-2, 7-8, 13-14, 19-20, 25-26, 31-32.
The report as to Inventive Step was positive (YES) with respect to claims 3-6, 9-12, 15-18, 21-24, 27-30, 33-42.
The report as to Inventive Step was negative (NO) with respect to claims 1-2, 7-8, 13-14, 19-20, 25-26, 31-32.
The report as to Industrial Applicability was positive (YES) with respect to claims 1-42.
The report as to Industrial Applicability was negative (NO) with respect to claims NONE.

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
increased transport of peptides across the endoplasmic reticulum as measured by increased surface expression of peptide loaded MHC class I molecules on the cell surface compared to untransfected B cells from the same source (Wang et al., supra, page 1007, figure 1, and pages 1008-1010). Thus, by teaching all the elements of the claims, Wang et al. both anticipates and makes obvious the instant invention.

Claims 3-6, 9-12, 15-18, 21-24, 27-30, and 33-42 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest an isolated nucleic acid encoding TAP2 exon 12, or teach an alternative splice variant of TAP2 which does not contain exon 11, but does contain exon 12 and which is encoded by SEQ ID NO. 4.

Claims 1-42 meet the criteria set out in PCT Article 33(4) for industrial applicability.

---------- NEW CITATIONS ----------
WANG et al. Tap-1 and Tap-2 Gene Therapy Selectively Restores Conformationally Dependent HLA Class I Expression in Type I Diabetic Cells. Human Gene Therapy. August 1995, Vol. 6, pages 1005-1017, see pages 1007-1010.

VIII. CERTAIN OBSERVATIONS ON THE APPLICATION (Continued):
any evidence that the additional intronic sequences are translated, and/or that the resulting TAP1 or 2 proteins are functional both in forming heterodimers with other wild type or splice variant TAP proteins and in transporting peptides across the ER. Further, the description does not demonstrate that any variant other than TAP2iso protein is capable of altering the specificity of peptide transport in a cell. It is also noted that the description provides no guidance or teachings that splice variants of TAP1 and TAP2 exist for any species other than humans. Thus, due to the lack of guidance provided by the description concerning the characteristics of splice variants of TAP1 and TAP2 other than human TAP2iso in terms of the physical characteristics of the nucleic acids themselves and their ability to generate functional TAP proteins as discussed above, it would have required undue experimentation for the skilled artisan to make or isolate the splice variants of the instant invention from any and all species. Further, based on the lack of teachings in the description or the prior art as to the existence of TAP splice variants in species other than humans, the skilled artisan would not have considered it predictable to make or isolate TAP splice variants from other species or to produce any and all TAP splice variant proteins capable of forming heterodimers with other normal or variant TAP proteins.

The description does not provide an enabling disclosure for altering peptide transport in any and all cells or for broadening an immune response to an antigen comprising transfecting any cell with an expression vector encoding any and all human TAP1 or TAP2 splice variants. As discussed in detail above, it is unclear from the description whether the human TAP1 splice variants or the TAP2iso2 variant detected by RT-PCR are actually translated into functional TAP proteins. Further, while the description teaches that multiple variants of the TAP1 and TAP2 mRNA are transcribed in many lymphoid cells, the description does not disclose that any combination of TAP1 protein and TAP2 protein translated from these various

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

mRNA species is capable of forming a functional heterodimer. In addition, besides the combination of TAP2iso and wild type TAP1, the description does not disclose the composition or characteristics of heterodimers that results in altered peptide transport compared to the wild type transport proteins. In regards to the TAP2iso, the description provides a working example demonstrating that the transfection of both wild type TAP1 and TAP2iso into the mutant cell line T2 results in restoration of MHC class I surface expression. The description clearly states that the transfection of TAP2iso alone had no effect on class I expression (description, page 25, lines 21-22). Thus, peptide transport requires the presence of both a TAP1 subunit and a TAP2 subunit in the cell. The working example also demonstrates that the transporter heterodimer formed with TAP1 and TAP2iso differs from the wild type transporter in its preference for transporting certain peptides. However, T2 cells lack TAP1 and TAP2 expression. The description does not disclose or demonstrate the ability of recombinant TAP2iso to affect peptide transport in the presence of wild type TAP2 and any endogenous amount of TAP2iso. The description is silent as to the affinity of TAP2iso for wild type TAP1 compared to that of wild type TAP2, for the ratio of wild type to variant transporter heterodimers formed in cells expressing both TAP2 and TAP2iso, and the overall effect on peptide transport in cells in which there are varying ratios of wild type TAP2 and TAP2iso containing transporter heterodimers. In the absence of any guidance from the description concerning these parameters, the skilled artisan would not be able to predict the effect of expressing human TAP2iso in a cell on peptide transport. Therefore, in view of the state of the art at the time of filing which does not teach that peptide transport can be altered in a cell by expressing a splice variant of a TAP protein, the lack of guidance provided by the description for the parameters discussed above, and the breadth of the claims, it would have required undue experimentation to practice the instant invention as claimed.

The description does not provide an enabling disclosure for treating any immune disorder associated with abnormal expression of a TAP heterodimer. The description postulates that autoimmune disease and cancer may be associated with the lack of expression of TAP1 and/or TAP2 and suggests that replacing TAP1 and/or TAP2 expression by administering an expression vector encoding a wild type or splice variant of TAP1 or TAP2 will result in therapy of the autoimmune disease or cancer. However, the description does not disclose or demonstrate the loss of any splice TAP1 or TAP2 variant and any autoimmune disease or cancer. In fact, the description demonstrates that at least for hypothyroid disease, there is not discernable difference in the expression of TAP2 variants in cells from patients with hypothyroidism than in normal cells. Further, although the art at the time of filing teaches that defective wild type TAP1 and/or TAP2 expression is associated with diabetes, it posits that the effects of defective TAP expression are associated with the abnormal development of autoimmune T cells due to the failure of negative selection, a process that occurs during childhood in the thymus. While the art does teach that MHC class I expression can be increased in diabetic patients by introduction of wild type TAP alleles, it does not suggest that diabetes can be treated by such therapy or demonstrate that increased TAP expression in diabetic patients results in tolerance, deletion, or inactivation of autoreactive T cells. Wang et al. also teaches that while, ".. altered class I presentation of self-peptides can lead to failed T cell education to self and development of autoimmunity,... multiple immunologic mechanisms likely contribute to the expansion and propagation of autoimmune disease" (Wang et al. (1995) Human Gene Therapy, Vol. 6, page 1016, paragraphs 2-3). Further, the description does not provide any guidance for the administration of expression vectors encoding TAP splice variants according to the instant invention, such as dosage, sites of administration, and mode of administration, or provide guidance as to the level of TAP expression required to result in any effect on any immune disorder. Thus, in view of the art recognized unpredictability of treating any immune disorder associated with abnormal TAP expression by administering TAP1 or TAP2, the lack of guidance provided by the description for the parameters discussed above, and the breadth of the claims, it would have required undue experimentation for the skilled artisan to practice the scope of the invention as claimed.

Claims 1-42 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not enabled as required under PCT Rule 5.1(a) for the reasons set forth in the immediately preceding paragraphs.

09/622,275

PATENT COOPERATION TREATY

PCT

RECD 12 DEC 2000

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

4

Applicant's or agent's file reference GEOSYS01.006	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/04528	International filing date *(day/month/year)* 02 MARCH 1999	Priority date *(day/month/year)* 03 MARCH 1998
International Patent Classification (IPC) or national classification and IPC IPC(7): G06F 17/30 and US Cl.: 707/206		
Applicant GEODESIC SYSTEMS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☐ Certain observations on the international application

Date of submission of the demand 23 SEPTEMBER 1999	Date of completion of this report 20 NOVEMBER 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer PAUL KULIK James R. Matthews Telephone No. (703) 305-3831

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/04528

I. Basis of the report

1. With regard to the elements of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-13, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the claims:
pages 14-25, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the drawings:
pages 1-7, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE
[X] the claims, Nos. NONE
[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/04528

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	1-47	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	1-47	YES
	Claims	NONE	NO
Industrial Applicability (IA)	Claims	1-47	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1-47 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the claimed (claims 1-40)automatic determination by examining a program that the program will use a resource and the automatic modification of the program's behavior such that the program's execution makes an entry for the resource in a registry. Likewise the prior art does not teach or fairly suggest, with respect to claims 41-47, the claimed automatic execution of a finalizer associated with an object, in conjunction with a program modifier that automatically modifies a program prior to its execution such that allocation of the object causes a registrar to register the object in a registry.

---------- NEW CITATIONS ----------

NONE

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07H 21/04, C12N 15/11, 15/63, 15/85, 1/21, C07K 5/00, 14/00, 16/00, A61K 48/00

A1

(11) International Publication Number: WO 99/52928

(43) International Publication Date: 21 October 1999 (21.10.99)

(21) International Application Number: PCT/US99/08205

(22) International Filing Date: 15 April 1999 (15.04.99)

(30) Priority Data:
09/061,764 16 April 1998 (16.04.98) US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 09/061,764 (CIP)
Filed on 16 April 1998 (16.04.98)

(71) Applicant *(for all designated States except US)*: THE GENERAL HOSPITAL CORPORATION [US/US]; 55 Fruit Street, Boston, MA 02114 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: FAUSTMAN, Denise, L. [US/US]; 74 Pinecroft Road, Weston, MA 02193 (US).

(74) Agent: YANKWICH, Leon, R.; Yankwich & Associates, 130 Bishop Allen Drive, Cambridge, MA 02139 (US).

(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: TRANSPORTER PROTEIN SPLICE VARIANTS AND MODEL FOR IMMUNE DIVERSITY

(57) Abstract

Splice variants of known TAP1 and TAP2 proteins, which are involved in translocation of antigen peptides into the endoplasmic reticulum for complexing with MHC class I molecules and eventual display on the cell surface, are disclosed. Two fully sequenced and characterized splice variants of TAP1 and TAP2, designated TAP1iso^3 and TAP2iso, respectively are disclosed. The TAP2iso protein subunit is shown to form functional heterodimers with TAP1 and to exhibit a peptide specificity that differs from previously studied TAP1/TAP2 transporter proteins. The discovery of splice variant TAP subunits alters the prior theory of immune response and introduces a cellular mechanism for diversification of antigen display to the CD8–positive T cells of the immune system. method for diagnosis and treatment of diseases or conditions associated with abnormal TAP isoform expression, or of expanding the repertoire of antigen peptides to which an individual's immune system is capable of responding, are also disclosed.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/08205

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :536/23.1; 435/320.1, 325, 252.3; 530/300, 350, 387.1; 514/44
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.1; 435/320.1, 325, 252.3; 530/300, 350, 387.1; 514/44

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DIALOG-Medline, Embase, Scisearch, Biosis, Cancerlit; APS, Derwint
search terms: TAP1, TAP2, splice variants, RING4, RING11

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	**BECK. S.** et al., DNA sequence Analysis of 66 kb of the human mhc class II region encoding a cluster of genes for antigen processing. J. Mol. Biol. 1992. Vol. 228. pages 433-441, especially page 437.	1-6 ----- 7-42
X --- Y	**POWIS. S.H.** et al., Alleles and haplotypes of the MHC-encoded ABC transporters TAP1 and TAP2. Immunogenetics. 1993. Vol. 37. pages 373-380, especially page 378.	1-6 ----- 7-42
X --- Y	**BAHRAM. S.** et al., Two putative subunits of a peptide pump encoded in the human major histocompatibility complex class II region. Proc. Natl. Acad. Sci. USA. November 1991. Vol. 88. pages 10094-10098, especially page10095.	1-6, 31-36 ---------- 7-30, 37-42

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
01 JULY 1999

Date of mailing of the international search report
23 AUG 1999

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/08205

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92/11289 A1 (IMPERIAL CANCER RESEARCH TECHNOLOGY LTD.) 09 July 1992, see entire document.	1-42

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/08205

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

C07H 21/04; C12N 15/11, 15/63, 15/85, 1/21; C07K 5/00, 14/00, 16/00; A61K 48/00